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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,675	02/12/2001	Nicholas C. Nicolaides	01107.00098	8276

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EXAMINER
AKHAVAN, RAMIN

ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/780,675	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ray Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,12,14-18,26,27 and 71-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-7, 12, 14-18, 26-27 and 71-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 8, 2003 (Paper No. 19) has been entered.

Response to Amendments

The rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Aronshtam et al. NAR (1996) 24: 2498-2504 (cited in IDS) has been withdrawn in view of applicant's amendment. In addition the rejection of claims 1 and 18 as anticipated by Prudhomme et al. J. Bacteriol (1991) 173: 7196-7203 is withdrawn. Furthermore the rejection of claims 12, 16 and 71 under 35 U.S.C. §112 ¶2 is withdrawn in light of applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 recite the limitation "mismatch repair gene" in claim 1. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite "gene" but rather recites the term "protein". Proper correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-7, 12, 14-16, 18, 26-27 and 71-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's invention relates to using a dominant negative allele of a mismatch repair gene, e.g. human PMS2 with truncation mutation at codon 134 (*hPMS2-134*) or *A. thaliana* PMS134-FLAG fusion (*ATPMS134*), which carries a truncation mutation at codon 134 to induce an increased rate of mutation in *any* bacteria transformed with said gene. Claim 1 is drawn to transforming bacteria with a gene that encodes "a form of PMS2 mismatch repair protein". Claim 6 is drawn to the human PMS2 gene and claim 7 to any plant PMS2 gene to effect the same function of hypermutability. Claims 12 and 14-15 each respectively depend from claims 1, 6 and 7 while adding the limitation that each gene comprises any truncation mutation. In addition claim 16 depends from claim 7 and adds the limitation that the PMS2 gene in any plant comprises a truncation mutation at codon 134.

Claim 18 is drawn to a genus of bacteria comprised of a polynucleotide encoding a form of PMS2 mismatch repair protein and where bacteria are hypermutable. Claims 26 and 27 are drawn to a genus of bacteria expressing a truncated PMS2 gene and where the protein is human PMS2.

Claims 71-73 are drawn to either methods (71-72) or compositions (73) that similarly are drawn to *any* bacterium made hypermutable using a polynucleotide encoding a form of PMS2 (71), polynucleotide encoding a mismatch repair protein selected from a group of PMSR and PMS2L (72), or cultured cells of any bacterium made hypermutable using polynucleotides selected from a group consisting of PMSR and PMS2L protein. The claims as written are drawn to either a of PMS2 genes from a disparate number of species or to a genus of bacteria or both. Thus the claims encompass a vast multitude of species. It would suffice to point out that the disclosure does not support the vast number of species of mismatch repair proteins nor bacteria to which the claims are drawn.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification is deficient in describing a structure-function relationship for all potential species of PMS2 genes. Concomitantly the specification is deficient in showing such a

relationship between the disclosed PMS2 and that said PMS2 would cause hypermutability in *any* bacterium.

Instead, the specification teaches that expression of *hPMS2-134* causes hypermutability in *E. coli* or that *ATPMS134* causes mutability (12 colonies versus none, Spec. at 25-26), but it is deficient in describing a structure-function relationship for human PMS2 with no mutation at codon 134 (claim 6) or any plant PMS2 (claim 7) or said genes with any truncation mutation (claim 14-15) or any plant PMS2 with a truncation at codon 134 (claim 16). As indicated to above, the specification does not teach that *hPMS2-134* would cause hypermutability in any bacteria (current estimations are that there are over 3 million marine species alone and about 4,000 that have been described). Claim 18 is drawn to both a genus of bacteria as well as a genus of mismatch repair protein ("form of....PMS2").

Claim 71 is drawn to any PMS2 protein while the specification only teaches *hPMS2-134* or *A. thaliana* PMS134-FLAG fusion (ATPMS134). Similarly claims 72-73 are drawn to any form of PMSR and PMS2L while the specification does not teach any species. In addition the claims are drawn to an entire genus (bacteria) while only a single species is disclosed. These genes represent embodiments not previously claimed however the analysis applied above with regard to PMS2 would just as aptly apply here if not more so; it would suffice it to say the specification does not teach a correlation between structure-function with regard to all PMSR and PMS2L genes. Results from human PMSR3 cannot be extrapolated to other genes in the PMSR family. The only disclosure with regard to PMS2L is that it is another member of the MMR family homologous to MutL. There is nothing in the specification to indicate to one of ordinary skill in the art that applicant was in possession of the subject matter to which claims 72

and 73 are drawn. In fact the function of PMSR genes is not definitively known. Nicolaides et al. Genomics (1995), at 205 (ref. cited in IDS by applicant).

In sum there is no disclosure of whether a truncation mutation at various locations in any PMS2 gene from any other species (other than *human* or *Arabidopsis*) would result in a dominant negative allele or a dominant negative effect when expressed in any bacterium. Furthermore, the disclosure is deficient in teaching that the truncated version of *hPMS2* or any form of PMS2, PMSR and PMS2L would cause hypermutability in any bacterium. The specification does teach methods for identifying dominant negative alleles and assays for dominant negative effect but such disclosure does not obviate a written description rejection and is only relevant to an enablement rejection.

Applicant submits that because mice that are nullizygous for the murine PMS2 gene showed elevation in mutation frequency in all tissues examined, then PMS2 proteins from disparate species would function in the same way. (Exhibit A and B in applicant's Remarks at p.15) This analogy is predicated upon a study where deletion of a mismatch repair protein caused hypermutability, not based on which domains of said protein are necessary for functionality. A relevant study would be one where clarification of functional domains from a representative number of species of mismatch repair proteins is shown to map to identical domains, i.e. showing structural-function correlation.

It would be evident to one of ordinary skill in the art that although genes from species share homology that the key to the structure-function correlation is in the various domains that confer functionality. Such clarification of the functional domains is not provided in the specification, nor is it supported in the reference submitted. *See* Aronshtam, NAR, 1996, 24(13):

2498 (noting the multifunctional MutS and MutL protein and that functional domains map throughout the gene). Thus the same mutation in the PMS2 (or other MMR) gene from one species will not necessarily correlate to an expected function (e.g. hypermutability) in any given bacterium. The knowledge in the art would indicate that functional domains would have to be clarified for a sufficient correlation between a known structure and an expected function. Such is not the case in instant application.

Conclusion

Claims 1, 6-7, 12, 14-18, 26-27 and 71-73 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

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DAVID GUZO
PRIMARY EXAMINER